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ORIGINAL ARTICLE

Prognostic significance of disordered calcium metabolism in hormone-refractory prostate cancer patients with metastatic bone disease

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Bone metabolic disruption that occurs in bone metastatic prostate cancer could lead to disturbances of calcium metabolism. The prognostic role of either hypocalcemia or hypercalcemia was assessed in a consecutive series of hormone-refractory bone metastatic prostate cancer patients. Serum calcium was measured in 192 patients. The presence of hypocalcemia and hypercalcemia was related with baseline biochemical and clinical characteristics and the role of these two calcium disturbances in predicting prognosis and adverse skeletal-related events (SREs) was assessed. As compared to normocalcemic patients, hypocalcemic patients ($n = 51$) had higher tumor load in bone ($P = 0.005$), higher plasma chromogranin A (CgA, $P = 0.01$), serum alkaline phosphatase ($P = 0.01$), urinary N-telopeptide (NTX, $P = 0.002$) and lower hemoglobin values ($P = 0.01$), while hypercalcemic patients ($n = 16$) had higher plasma CgA ($P = 0.001$) and serum lactate dehydrogenase values ($P = 0.001$), higher bone pain ($P = 0.003$) and a lower frequency of pure osteoblastic lesions ($P = 0.001$). Hypercalcemia was significantly associated with poor prognosis: hazard ratio (HR), 1.9 (95% confidence Interval (CI) 1.2–3.3) and higher risk to develop SREs HR, 2.5 (95% CI 1.2–5.2, $P = 0.01$), while hypocalcemia was not associated with poor prognosis. The prognostic role of hypercalcemia was maintained in multivariate analysis after adjusting for validated prognostic parameters: HR, 2.72 (95% CI 1.1–6.8, $P = 0.03$). These data suggest that serum calcium levels should be taken into account in the clinical decision-making process of bone metastatic prostate cancer patients. Patients with asymptomatic hypercalcemia could benefit of a strict follow-up and an immediate bisphosphonate treatment. Further prospective clinical trials are needed to confirm this finding.
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Introduction

Prostate cancer is the leading malignancy in the aging male population[1] and skeleton is the most frequent site of metastatic disease.[2] Metastatic cancer cells in bone microenvironment release a number of cytokines and growth factors that stimulate dysregulated bone resorption and bone formation resulting in lytic bone lesions, blastic bone lesions or both.[2] Metastatic bone lesions from prostate cancer are typically osteoblastic.

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The osteoblastic nature of bone lesions not withstanding, osteolysis is a regular feature in bone metastatic prostate cancer patients and may cause skeletal morbidity.[3] Increased osteoclast activity is not only confined to metastatic sites, but may be also a generalized phenomenon related to secondary hyperparathyroidism as a consequence of the so-called bone hunger syndrome[3,4] and due to osteoporosis induced by androgen deprivation.[3] Androgen deprivation is the mainstay of therapy of advanced prostate cancer, this treatment leads to serological and clinical improvement in more than 90% of patients.[5] Androgen deprivation therapy is not curative and the majority of patients are destined to progress to hormone-refractory disease. The prognosis of hormone-refractory patients is dismal and the overall survival is about 13–16 months on average.[6,7] The relatively long survival of these patients, however, facilitates the onset of skeletal complications.[3] Until the

disease is responsive to androgen deprivation, adverse skeletal events and metabolic disturbances are rare.[8] However, they are more frequent when the tumor become refractory to hormone manipulations.[8]

Calcium homeostasis is a tightly regulated process involving the coordinated efforts of the skeleton, kidney, parathyroid glands and intestine. Cancer cells adversely affect mineral metabolism through a broad spectrum of mechanisms.[9] Neoplasms can cause hypercalcemia through the production of endocrine factors, notably parathyroid hormone-related peptides (PTHrP). Hypercalcemia typically complicates the natural history of bone metastatic patients with predominantly lytic bone lesions, such as those with breast and lung cancer.[9] In patients with prostate cancer this metabolic disturbance has been described exceptionally.[10–13] A number of factors could prevent the onset of hypercalcemia in prostate cancer patients. The osteoblastic nature of bone lesions could lead to calcium entrapment in bone.[3,4] PTHrP may be produced by prostate cancer[14] but the prostate-specific antigen (PSA), which is a kallikrein enzyme widely expressed by prostate cancer cells, is able to cleave it.[15]

By contrast, the bone hunger syndrome induced by prostate cancer bone metastases could predispose patients to hypocalcemia and secondary hyperparathyroidism in response to the increased calcium demand.[3,4]

Few papers, which are case reports or series of symptomatic cases, reported data on hypercalcemia in patients with prostate cancer.[10–13] To our knowledge no data are available on prevalence of supranormal calcium levels in advanced prostate cancer population. The prevalence of hypocalcemia in bone metastatic prostate cancer patients has been reported in one study showing that 43 of 131 patients (33%) had calcium levels below the normal range.[16] The prognostic impact of either hypocalcemia or hypercalcemia has never been described, to the best of our knowledge.

In this study, the frequency of hypocalcemia and hypercalcemia was evaluated in a series of hormone-refractory prostate cancer patients with metastatic bone disease prospectively followed at the Prostate Cancer Unit of the Azienda Ospedaliera San Luigi di Orbassano, Italy. The primary aim of this study was to evaluate the prognostic role of these metabolic disturbances, secondary aims were to evaluate the relationship of hypocalcemia and hypercalcemia with commonly recognized prognostic parameters and to assess the role of these disturbances in predicting adverse skeletal-related events (SREs).

Materials and methods

Patients

Eligible patients were required to meet the following inclusion criteria: histologically proven adenocarcinoma of the prostate, metastatic bone disease as assessed by bone scan followed by radiological confirmation of hot spots, disease progression to androgen deprivation therapy defined as a rise in PSA levels of 50% or more over the nadir obtained during androgen deprivation therapy on two consecutive measurements performed at least 2 weeks apart, or a new lesion on bone scan and/or an increase in the size of a measurable lesion on a computed tomographic (CT) scan of the abdomen/pelvis or chest. The time from diagnosis of hormone refractoriness to enrollment in the study should have been not greater than 2 months.

Patients previously treated with luteinizing hormone-releasing hormone analogues (LHRH-A) alone underwent total androgen ablation by adding an antiandrogen (flutamide or bicalutamide). They entered the study if they showed further evidence of disease progression after at least 4 weeks of combined therapy. Patients previously treated with total androgen ablation were required to undergo antiandrogen withdrawal. They were required to be off all antiandrogen for at least 4 weeks, with further evidence of disease progression after cessation of antiandrogen treatment. Serum testosterone was routinely measured in all patients showing PSA progression under LHRH-A since 1997.

From this date onward testosterone inhibition (defined as serum levels <50 ng per 100 ml) was added to the criteria of hormone refractoriness. Further inclusion criteria consisted an Eastern Cooperative Oncology performance status (PS) of 0–3 and normal renal and hepatic function. Patients were excluded from the study if they had severe uncontrolled comorbidity, second malignancies, pretreatment with bisphosphonates, radiotherapy or radionuclide therapy for palliation of bone pain, and second-line antineoplastic treatment. At study entry, all patients underwent physical examination, including bone pain assessment, routine blood chemistry studies, serum PSA, serum alkaline phosphatase (ALP), plasma chromogranin A (CgA, the last 106 patients), bone scan followed by radiological confirmation of hot spots, chest X-ray and whole-abdomen CT, urinary N-telopeptide (NTX, the last 103 patients). The whole skeleton was arbitrarily divided into the following areas: skull, cervical, dorsal, lumbar spine + sacrum, right leg, left leg, right arm, left arm, right ribs, left ribs, sternum, right scapula and clavicula, left scapula and clavicula, right pelvis and left pelvis. Disease extent in bone was calculated as the sum of involved areas. Baseline bone pain was evaluated using a validated pain questionnaire, as previously reported.[8] Items included PS, analgesic consumption and mobility, as measured on a pain score of 0–19. All patients subsequently received second-line treatments consisting of endocrine therapy, chemotherapy, radiotherapy and radionuclide therapy, as indicated in association with the best palliative care.

Study end points

Survival duration was defined as the time between the diagnosis of hormone-refractory disease and death. Patients were censored if they were known to be alive or were lost to follow-up. SREs were defined as vertebral body collapse requiring spinal orthosis, spinal cord compression, and vertebral and non-vertebral pathologic fractures. The time to the onset of skeletal complications was calculated as the time between the diagnosis of hormone-refractory disease and the occurrence of the first SRE or death, whichever event occurred first. Patients were censored if they were alive and free of SREs.

Biochemical measurements

Early morning spot urine specimens were obtained to measure creatinine and NTX; blood samples were drawn to assess calcium, albumin, PSA, total ALP, lactate dehydrogenase (LDH), hemoglobin and CgA. NTX was measured using a commercial kit (Osteomark, Ortho-Clinical Diagnostics, Rochester, NY, USA), plasma CgA was measured using an enzyme-linked immunosorbent assay kit (Dako, Glostrup, Denmark) serum PTH (intact molecule) was measured by an immunoradiometric assay (Nichols, San Juan Capistrano, CA, USA) that does not cross-react with PTHrP.[17,18] Measuring ranges, minimum detectable concentrations, intra- and inter-assay coefficients of variation were as follows: NTX 30–3000 nM, 20 nM, 4.4 and 6.9%; CgA 5–650 $U\,l^{-1}$, 2 $U\,l^{-1}$, 4.7 and 5.6%; PTH 2.5–2000 $pg\,ml^{-1}$, 2.1 $pg\,ml^{-1}$, 4.1 and 4.9%.

The remaining blood biochemical parameters, including calcium, were measured using automated procedures (Architect, Abbott, Rome, Italy). Calcium levels were corrected for serum albumin; normal level was defined as the range between 2.20 and 2.65 $mmol\,l^{-1}$, values above and below this range were considered as hypercalcemia and hypocalcemia, respectively.

Statistical analysis

Differences in proportion were determined using the χ^2-test. Comparison of continuous variables was performed using Mann–Whitney *U*-test for nonparametric data. Survival curves were estimated using the Kaplan–Meier method. A univariate Cox proportional hazards model was used to assess whether hypocalcemia and hypercalcemia were statistically significant predictors of SREs and death. A multivariate Cox proportional hazards model was used to identify independent variables predictive of survival and onset of SREs. Serum ALP, serum PSA and serum LDH had right-skewed distributions and were modeled using log transformation. All reported *P*-values were two sided; *P*-values <0.05 were considered statistically significant. Statistical computation was performed using the SPSS for Windows software package.

Results

From July 1990 to June 2003, 210 consecutive patients with newly diagnosed hormone-refractory prostate cancer met the inclusion criteria. Among them, 192 had serum calcium assessed at baseline condition and entered the present study. Patient characteristics are depicted in Table 1. Most of patients had blastic bone lesions, one-third had lytic/mixed bone lesions. Albumin-corrected serum calcium levels were above the normal range in 16 patients (8.3%) and below the normal range in 51 patients (26.6%). One-third of patients received chemotherapy, and two-thirds steroids plus supportive care. A total of 32 patients received a single-dose pamidronate.[19] Previous LHRH-A administration was not interrupted in all cases.

After a median follow-up of 38 months, 167 patients died (87.0%) and 84 patients (43.8%) experienced skeletal complications: vertebral collapse in 41 (21.4%), fractures in 24 (12.5%) and spinal cord compression in 19 (9.8%). Three patients had symptomatic hypercalcemia, and one patient had symptomatic hypocalcemia.

Table 1 Patient characteristics

No	192
Age[a]	73 (52–92)
Performance status (%)	
0–1	129 (67.2)
2–3	63 (32.8)
Type of bone lesions (%)	
Lytic/Mixed	55 (28.8)
Blastic	128 (67.0)
Bone scan+/Rx−	8 (4.2)
Number of skeletal segment involved (%)	
$\leqslant 3$	72 (37.3)
4–6	38 (20.0)
>6	82 (42.7)
Visceral metastases *(%)*	20 (10.4)
Pain score[a]	5 (0–16)
Calcium ($mmol\,l^{-1}$)[a]	2.36 (1.91–4.20)
Hypocalcemia *(%)*	51 (26.6)
Normocalcemia *(%)*	125 (65.1)
Hypercalcemia *(%)*	16 (8.3)
PTH ($pg\,ml^{-1}$)[a]	49 (3.0–267.0)
Missing 41	
Markers	
CgA (U^{-1})[a]	17.4 (3.0–394.0)
Missing 86	
NTX (nM BCE/mmol CrU)[a]	101.5 (13.3–679.0)
Missing 84	
ALP ($U\,l^{-1}$)[a]	162.0 (47.0–6000.0)
Missing 4	
PSA ($ng\,ml^{-1}$)[a]	118 (0.1–9.000.0)
Missing 5	
Hb (g per 100 ml)[a]	12.1 (7.3–15.6)
Missing 28	

Abbreviations: ALP, alkaline phosphatase; BCE, bone collagen equivalents; CgA, chromogranin A; Hb, hemoglobin; NTX, N-telopeptide; PSA, prostate-specific antigen; PTH, parathyroid hormone.
[a]Data are median and range.

Relationship between calcium unbalances and clinical and biochemical characteristics

Table 2 depicts the distribution of clinical and biochemical variables according to calcium level status. As expected, hypocalcemia was associated with greater PTH levels and hypercalcemia with lower PTH values than normocalcemia. Noteworthy, the great majority of hypercalcemic patients had serum PTH at the inferior limit of normality, two patients however showed elevated PTH levels. These data suggest primary hyperparathyroidism. As compared to normocalcemic patients, patients with hypocalcemia had higher plasma CgA, serum ALP, urinary NTX and lower hemoglobin values. They also had a greater frequency of high tumor load in bone. No difference in serum PSA, serum LDH, Gleason score, bone pain and type of bone lesions was observed between hypocalcemic and normocalcemic patients.

Table 2 Variables distribution according to calcium level status

	Hypocalcemia	*Normocalcemia*	*Hypercalcemia*
PTH(pg ml^{-1})[a]	67.0 (10.0–267.0)	45.5 (10.0–199.0)	29.3 (3.0–115.0)
P[b]	0.008		0.01
CgA(U l^{-1})[a]	25.5 (5.2–302.0)	12.0 (3.0–394.0)	72.8 (3.0–174.0)
P[b]	0.01		0.02
LDH(U l^{-1})[a]	464.5 (166.0–2425.0)	406 (136.0–1940.0)	732.5 (366.0–3011.0)
P[b]	0.15		0.001
PSA(ng ml^{-1})[a]	100.0 (0.3–3393.0)	118 (0.1–9000.0)	200.0 (0.1–9000.0)
P[b]	0.90		0.23
Hb(g per 100 ml)[a]	11.8 (7.7–15.6)	12.5 (7.3–15.6)	10.9 (9.3–14.8)
P[b]	0.013		0.16
ALP(U l^{-1})[a]	205.0 (47.0–6000.0)	137.0 (48.0–2486.0)	218.5 (47.0–2560.0)
P[b]	0.015		0.14
NTX[a]			
(nM BCE/mmol CrU)	191.0 (32.3–679.0)	96.2 (13.3–662.0)	145.3 (67.5–356.0)
P[b]	0.002		0.08
PAIN score[a]	5.5 (0–13)	5.0 (0–16)	8 (2–15)
P[b]	0.30		0.003
Gleason score >7	30/51 (58.8%)	56/125 (44.8%)	12/18 (66.6%)
P[b]	0.09		0.08
Visceral disease	6 /51 (11.8%)	14/124 (11.3%)	0/17 (0%)
P[b]	0.92		0.21
High bone[c]			
Tumor load	30/51 (58.8%)	44/123 (35.8%)	8/17 (47.1%)
P[b]	0.005		0.37
Blastic bone lesions	37/51 (72.5%)	86/123 (69.9%)	5/17 (29.4%)
P[b]	0.73		0.001

Abbreviations: ALP, alkaline phosphatase; BCE, bone collagen equivalents; CgA, chromogranin A; Hb, hemoglobin; LDH, lactate dehydrogenase; NTX, N-telopeptide; PSA, prostate-specific antigen; PTH, parathyroid hormone.
[a]Data are median and range.
[b]Statistical comparison of hypo or hypercalcemia versus normocalcemia.
[c]>6 bone metastatic sites.

Hypercalcemic patients had higher plasma CgA and serum LDH values, higher bone pain and a lower frequency of pure blastic bone lesions than normocalcemic patients while there was no differences between the two groups in terms of serum ALP, urinary NTX, hemoglobin, serum PSA and Gleason score.

Predictive value of hypocalcemia and hypercalcemia on patient outcome

Hypocalcemia and hypercalcemia conditions were also analyzed to assess their predictive role with respect to two outcome end points: death and onset of adverse skeletal events.

Hypercalcemia was significantly associated with an increased risk of either undergoing adverse skeletal events or death, while hypocalcemia was not significantly associated with the two outcome end points (Figure 1). The prognostic role of hypercalcemia was also maintained in multivariate analysis after adjusting for validated prognostic parameters such as Gleason score, serum PSA, presence of visceral metastases, serum ALP, serum LDH and hemoglobin (Table 3).

Discussion

In cancer patients with bone metastases the focal disruption of bone remodeling processes and the systemic releases of calcium trophic hormones such as PTHrP could lead to unbalances in calcium metabolism.[9] The osteoblastic nature of secondary bone lesions and the relative low frequency of PTHrP elevation due to PSA cleavage predispose bone metastatic prostate cancer patients to hypocalcemia, whereas hypercalcemia is expected to be very rare. In our series of patients in which albumin-corrected serum calcium levels were systematically measured at the onset of hormone-refractory disease, hypocalcemia was observed in about 27% and hypercalcemia in 8.3% of cases, confirming the expectations. The frequency of hypocalcemic patients observed in the present study was similar to that observed by Murray *et al*. (32%)[16] but the proportion of hypercalcemic ones seems to be higher than the 0.5% estimated in a comprehensive survey.[10,12] While in the paper by Murray *et al*. serum calcium levels were measured in a consecutive series of cases as in the present study, only symptomatic cases were included in the previously mentioned survey and this is likely to account for the discrepancies observed.

Hypocalcemic patients had higher PTH levels than patients with normocalcemia in keeping with the pathophysiology of the so-called bone hunger syndrome.[3,4,8] Hypercalcemia in malignancy is mainly due to the tumor production of PTHrP.[9] We disclose the limit of not having measured PTHrP but the low PTH levels observed in our hypercalcemic patients are consistent with PTHrP elevation since the IRMA assay we used for PTH evaluation does not cross-react with PTHrP.[9,17,18] Out of 151, two patients (1.3%), however, had elevated levels of both serum calcium and PTH suggesting primary hyperparathyroidism. Hyperparathyroidism is frequent in the aged population,[20] thus the association

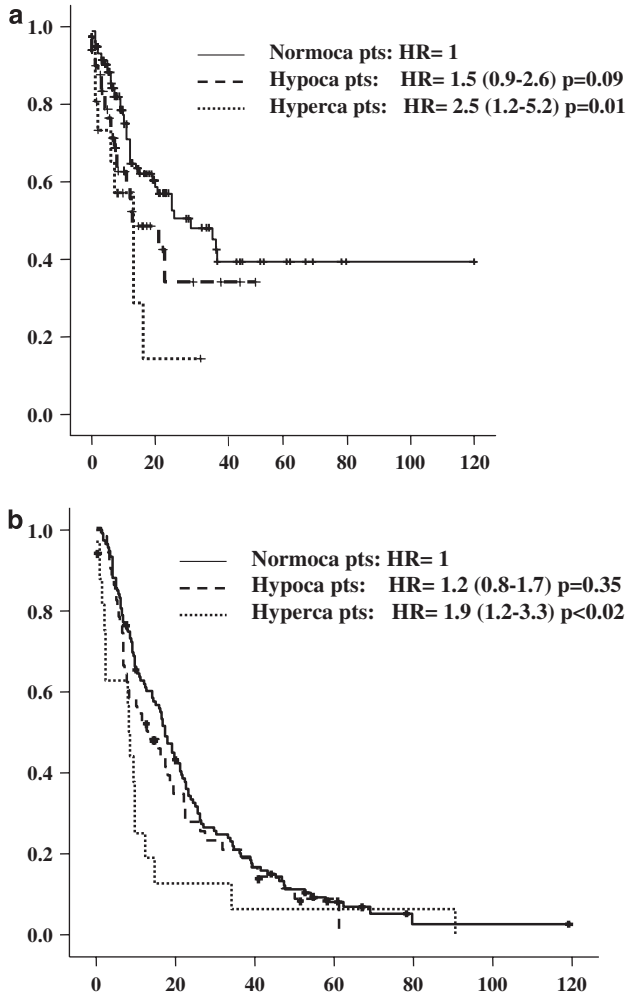

Figure 1 Time to first skeletal-related event (**a**) and overall survival (**b**) of bone metastatic prostate cancer patients according to calcium level status. Hazard ratio (HR, 95% confidence interval): HR of hypocalcemic and hypercalcemic patients with respect to patients with normocalcemia.

with prostate cancer is not expected to be rare even if precise estimates are not presently available. It has been reported that PTHrP production in prostate cancer patients correlates with the coexistence of neuroendocrine phenotype.[21] In the 106 patients in which plasma CgA was available, both hypercalcemic and hypocalcemic patients had higher CgA values than normocalcemic patients. Our data suggest that neuroendocrine phenotype is associated with a greater frequency of calcium unbalances but not necessarily with hypercalcemia.

Metastatic bone lesions of prostate cancer are typically osteoblastic, but bone lesions in patients with hypercalcemia were predominantly lytic/mixed. These data suggest that prostate cancer biology of patients with hypercalcemia may differ from that of normocalcemia or hypocalcemia. In the present study, both hypercalcemia and hypocalcemia correlated with some validated prognostic parameters suggesting that both disturbances may potentially identify patient subgroups with worse prognosis than normocalcemic patients. However, outcome

Table 3 Independent prognostic variables associated with overall survival

	HR (95% confidence interval)	P
Log ALP	1.39 (1.10–1.77)	0.012
Log LDH	1.80 (1.20–2.71)	0.005
Hb	0.80 (0.72–0.90)	0.000
Gleason score	1.17 (0.99–1.39)	0.06
Serum Ca	2.72 (1.08–6.84)	0.034
Variables not in the model		
Visceral metastases	1.22 (0.68–2.18)	0.52
Log PSA	1.04 (0.96–1.12)	0.36

Abbreviations: ALP, alkaline phosphatase; Hb, hemoglobin; LDH, lactate dehydrogenase; PSA, prostate-specific antigen.

analyses showed that hypercalcemia was correlated with higher risk of adverse skeletal events and death but hypocalcemia was not. Noteworthy, the prognostic role of hypercalcemia was maintained after adjusting for validated prognostic parameters suggesting that this metabolic disturbance should be added in the prognostic nomograms recently developed,[6,7] a finding that needs confirmation.

To conclude, calcium unbalance is a frequent condition in hormone-refractory prostate cancer patients with metastatic bone disease. Most patients had hypocalcemia, but the frequency of hypercalcemia was greater than expected if asymptomatic cases are included. The condition of hypercalcemia, whether symptomatic or not, identifies a patient subset with predominantly lytic/mixed bone lesions that are at higher risk of developing SREs and death. This is a retrospective study with 192 patients recruited over a long time, during which some changes occurred in clinical practice, this represents a limitation and caution should be adopted in generalizing the results. Our findings should be prospectively evaluated in future clinical trials. These hindrances notwithstanding physicians should to take into account serum calcium levels in the clinical decision-making process of prostate cancer patients with metastatic bone disease. Patients with hypercalcemia could benefit of a strict follow-up and may require an immediate bisphosphonate treatment.

Author contributions

Tucci, Mosca and Berruti had full access to all of the data in the study and takes responsibility for the accuracy of the data analysis.

Study concept and design: Tucci, Berruti, Mosca, Porpiglia and Terzolo.

Acquisition of data: Vana, Russo, Cracco and Lamanna.

Drafting of the manuscript: Berruti Tucci, Tampellini and Mosca.

Critical revision of the manuscript for important intellectual content: Dogliotti, Angeli and Scarpa.

Statistical analysis: Gorzegno and Tampellini.

PTH and Plasma Chromogranin assessment: Torta.

Other biochemical markers: Poggio and Reimondo.

Investigators enrolling and following the patients: Cracco, Tucci, Russo, Vana and Porpiglia.

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